Alternative splicing regulates mouse embryonic stem cell pluripotency and differentiation.

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Public Summary:
Two major goals of regenerative medicine are to reproducibly transform adult somatic cells into a pluripotent state and to control their differentiation into specific cell fates. Progress toward these goals would be greatly helped by obtaining a complete picture of the RNA isoforms produced by these cells due to alternative splicing and alternative promoter selection since this way we would have a more complete picture of the diversity of protein expression and how it is controlled within the cell. This paper catalogued the alternative splicing and promoter selection during heart muscle cell formation, revealing that many proteins are indeed controlled by splicing, creating alternative forms and also enabling differential regulation by miRNAs directed at some but not other splice variants.

Scientific Abstract:
Two major goals of regenerative medicine are to reproducibly transform adult somatic cells into a pluripotent state and to control their differentiation into specific cell fates. Progress toward these goals would be greatly helped by obtaining a complete picture of the RNA isoforms produced by these cells due to alternative splicing (AS) and alternative promoter selection (APS). To investigate the roles of AS and APS, reciprocal exon-exon junctions were interrogated on a genome-wide scale in differentiating mouse embryonic stem (ES) cells with a prototype Affymetrix microarray. Using a recently released open-source software package named AltAnalyze, we identified 144 genes for 170 putative isoform variants, the majority (67%) of which were predicted to alter protein sequence and domain composition. Verified alternative exons were largely associated with pathways of Wnt signaling and cell-cycle control, and most were conserved between mouse and human. To examine the functional impact of AS, we characterized isoforms for two genes. As predicted by AltAnalyze, we found that alternative isoforms of the gene Serca2 were targeted by distinct microRNAs (miRNA-200b, miRNA-214), suggesting a critical role for AS in cardiac development. Analysis of the Wnt transcription factor Tcf3, using selective knockdown of an ES cell-enriched and characterized isoform, revealed several distinct targets for transcriptional repression (Stmn2, Ccnd2, Atf3, Klf4, Nodal, and Jun) as well as distinct differentiation outcomes in ES cells. The findings herein illustrate a critical role for AS in the specification of ES cells with differentiation, and highlight the utility of global functional analyses of AS.

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